MRI/MRS of ischemic evolution in mouse brain at 14.1 T

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INTRODUCTION The study of stroke and development potential therapeutic approaches is of critical interest in contemporary medicine. Mouse models of stroke are an attractive approach to help understand the pathogenesis and establish potential therapeutic targets. MRI and MRS are ideally investigational tools suited to study the ischemic evolution events (1). For instance, T_2-weighted images are widely used for evaluating ischemic lesion size and neurochemical profile could specify underlying ischemic brain damage and its potential reversal. However, in mice, the brain size is small and only few studies have been reported neurochemical profiles at 9.4 Tesla. With the recent availability of a horizontal bore 14.1 Tesla system, the aim of the current study, therefore, was to demonstrate the feasibility of studying mouse stroke models at 14.1 Tesla.

METHODS Four iCR-CD1 mice (~25g) underwent 30 minutes endoluminal middle cerebral artery occlusion (MCAo) by filament techniques (3). The reduction in regional blood flow was assessed by laser-Doppler flowmetry with a flexible probe fixed on the skull and its reestablishement up to 10 minutes after terminating ischemia. Thereafter, animals were maintained in an incubator at 31°C. 8 and 24 hour following the ischemic insult, MR studies were performed in a horizontal 14.1T/26cm magnet (Varian/Magnex). Throughout the MR studies, the animals were anesthetized under 1-2% isoflurane to minimize potential motion with continous monitoring of temperature and breathing (SA instruments). The extent of the lesion was determined on FSE images (0.8-mm slice thickness, 24×24mm^2 FOV, 256^2 data matrix, TE_{eff}=50ms (ETL=8) and TR=5sec). Following adjustment of 1st and 2nd order shim currents using FASTESTMAP (4), localized spectra (6-8 µl) were obtained using SPECIAL (5) using 320 averages (TR=4s). Absolute quantification was achieved using LCModel resulting in a neurochemical profile consisting of 22 metabolite concentrations (in Table 1). For control values, in addition to the contralateral unaffected side (n=5) and two additional healthy mice were measured.

RESULTS AND DISCUSSION During ischemia, absolute rCBF dropped to 21±6% of control and recovered back to 70±24% shortly after stroke. T_2-weighted FSE images at 14.1 T readily depicted the extent of the stroke at 8 and more prominently at 24h (Fig. 1) consistently affecting the ipsilateral striatum and the cortex with more variability. Following shimming, the average linewidth in the striatum was 22Hz corresponding to 0.035 ppm. With a SNR of ~13. Cramer-Rao lower bounds were typically below 15% for 16 metabolites (mostly within 5%) except some other metabolites, such as Ace, Asc, Asp, Glc, PCho and Scyllo. Visually apparent changes in Fig 2, included Lac increased severalfold to10.0±2.3 mM, Gln concentration was doubled to 6.9±1.3 mM, NAA decreased to 3.6±1.2mM, as well as more modest decreases in Tau, Glu, when compared to control (n=7), whereas the macromolecule signal (attributed to cytosolic proteins) remained nearly constant (Table 1). In addition, a significant signal intensity was discernible at 1.9 ppm attributed to elevated acetate, which likely a degradation product of NAA. At 24 hr, more metabolites were found significantly changes, such as GABA, GPC, Gly, GSH, Ins, and PCr etc (Table 1). Ischemia results in profound changes in the neurochemical profile with a complex evolution pattern. Even at 8hr, the significant abnormality in the neurochemical profile was observed consistently but not all T_2-weighted images. Among the changes observed, the increased Gln is postulated to reflect excess glutamate excitotoxity. We conclude that both MRI and MRS are feasible in ischemic mouse brain at 14.1T. Additionally, the capabilities of measuring the neurochemical profile permit the detection of early biochemical response to ischemia.

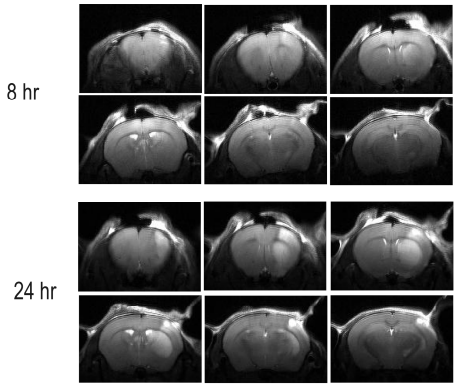

Figure 1. FSE multi-slice images of one ischemia mice 8hr and 24hr after stroke. The images were acquired 0.8-mm slice thickness and 0.2 mm gap with TE_{eff}=50ms (ETL=8) and TR= 5sec in a FOV of 24×24mm^2 with a 256^2 data matrix. The left captions specify the time after the onset of ischemic stroke. The black holes on top of the mice brains could be explained by the flow dometry placement before.

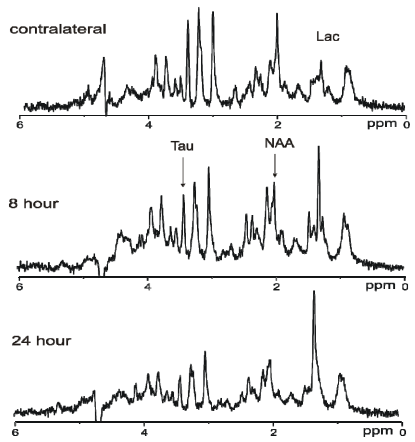

Figure 2. Localized spectra of one mouse striatum after ischemic stroke over time. TE=2.8ms, TR=4sec, nt=320 and 2×2×2 mm^3 VOI (in this particular mouse). Spectra were displayed after gauss apodization (gf=0.11, gfs=0.05). After 8 hr, Tau and NAA were found reduced Lac was increased. By removing possibilities of increased NAA and Glu (2.34 ppm), Gln (2.46 and 2.15 ppm) was visually confirmed increased, which is consistent with LcModel results, shown as in Table 1.

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Metabolite	~8hr (n=4)	~24hr (n=4)	Control (n=7)
Ace	0.4 ± 0.2	0.2 ± 0.2	0.0 ± 0.0
Ala	2.8 ± 0.8	2.2 ± 1.4	1.7 ± 0.6
Asc	0.1 ± 0.6	0.6 ± 0.7	1.3 ± 0.5
Asp	0.9 ± 0.7	1.1 ± 0.4	0.9 ± 0.5
Cr	3.0 ± 0.7	2.7 ± 1.0	3.5 ± 0.4
GABA	1.4 ± 0.6	0.8 ± 0.2 *	2.0 ± 0.4
Glc	0.6 ± 1.0	1.4 ± 0.4	0.7 ± 0.6
Gln	6.9 ± 1.3 *	2.2 ± 1.4	3.5 ± 0.5
Glu	5.0 ± 1.0	6.1 ± 1.1	7.5 ± 0.6
Gly	1.3 ± 0.2	1.1 ± 0.3 *	1.7 ± 0.4
GPC	0.0 ± 0.4	0.0 ± 0.1 *	0.5 ± 0.2
GSH	0.2 ± 0.6	0.1 ± 0.1 *	1.4 ± 0.2
Ins	2.8 ± 1.6	2.3 ± 0.5 *	3.9 ± 0.4
Lac	10.0 ± 2.3 *	11.1 ± 1.2 *	2.7 ± 1.2
Mac	1.3 ± 0.1	1.1 ± 0.2 *	1.4 ± 0.0
NAA	3.6 ± 1.2 *	2.1 ± 0.8 *	6.3 ± 0.3
NAAG	0.7 ± 0.1	0.6 ± 0.3	0.7 ± 0.2
PCho	0.2 ± 0.1	0.2 ± 0.2	0.4 ± 0.2
PCr	2.5 ± 0.9	1.9 ± 1.2 *	3.6 ± 0.6
PE	1.7 ± 0.2	1.9 ± 1.1	2.1 ± 0.6
Scyllo	0.1 ± 0.1	0.0 ± 0.0 *	0.2 ± 0.1
Tau	8.1 ± 1.4 *	4.3 ± 1.4 *	13.1 ± 1.4

Table 1. LcModel analysis results from the obtained spectra, such as shown in Fig.2. "~8hr" and "24hr" indicated the acquisition time of ^{1}H MRS data after the onset of ischemic stroke (0 hr), described in methods. Data were shown in mean ± SD with specific number of measurements ("n" in table). The significance (* on the corresponding right side) was found to the control when P <0.05 using two-tail unpaired student ttest.

References:

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